Protocol Number: VPED-102

Official Title: A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Adolescents with Symptomatic Gastroesophageal Reflux Disease

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Phathom Pharmaceuticals, Inc

VPED-102

A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Adolescents with Symptomatic Gastroesophageal Reflux Disease

31JAN2023

Statistical Analysis Plan

Version 2.0

Prepared by:

[redacted]

[redacted] | [redacted] Biostatistics and Programming

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**Phathom Pharmaceuticals, Inc**
Protocol Number:	**VPED-102**

Document Description:	Final Statistical Analysis Plan
SAP Title:	A Phase 1, Randomized, Parallel-group, Open-label, Multicentre Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Adolescents with Symptomatic Gastroesophageal Reflux Disease
SAP Version Number:	2.0
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Author(s):

[redacted], **Biostatistician II**

Approved by:

[redacted]

[redacted]

Summary of Changes

The VPED-102 protocol was amended on 14 September 2022 (Version 3.0, Amendment 2). Changes in that amendment are reflected in this document with a summary of the relevant protocol changes which precipitated modifications in the Statistical Analysis Plan presented below. The actual changes to the analyses are reflected in the respective sections in this document.

Amendment History and Reasons for Amendment

Version	Date	Reasons for Amendment
Version 1.0	01 November 2021	Original Statistical Analysis Plan
Version 2.0 (Based on Protocol Amendment 2)	31 January 2023	• Modified strategy to estimate PK parameters to a population based approach; as a result adjusted PK sampling schedule on Day 7, added PK sampling on Day 14, provided information on when time of dosing and meals should be collected and removed $T_{max,ss}$ and $t_{1/2z}$ PK parameters. • Moved symptom assessments and completion of PGSQ-A-SF questionnaire from Day 8 to Day 7 • Updated Schedule of Events and Study Design to reflect above changes

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List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BLQ	below the limit of quantification
CRF	Case Report Form
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
EE	erosive esophagitis
GERD	gastroesophageal reflux disease
GGT	gamma-glutamyl transferase
H+, K+-ATPase	hydrogen, potassium–adenosine triphosphatase
H2RA	histamine-2 receptor antagonist
hCG	human chorionic gonadotropin
IRT	interactive response technology
LFT	liver function test
MedDRA	medical Dictionary for Regulatory Activities
PGSQ-A-SF	Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form
PK	pharmacokinetic
popPK	population pharmacokinetic
PPI	proton pump inhibitor
PT	preferred Term
PTE	pretreatment event
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoE	schedule of events
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1. Introduction

Vonoprazan belongs to a new class of acid-inhibitory agents called "potassium-competitive acid blockers". Vonoprazan is being developed in adults for the treatment of heartburn in subjects with symptomatic non-erosive GERD, healing of all grades of EE and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, and treatment of Helicobacter pylori infection.

The purpose of this study is to determine a dose of vonoprazan in adolescent subjects with symptomatic GERD that provides an exposure similar to the exposures in adults after administration of vonoprazan 10 mg or 20 mg once daily (QD).

The pediatric doses for this study were selected to approximate equivalent adult exposures following administration of vonoprazan 10 or 20 mg QD and are age-based for adolescents 12 to 17 years of age.

This document outlines the statistical methods to be implemented in the analysis of data collected within the scope of Phathom Pharmaceuticals, Inc., Protocol VPED-102 (A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Adolescents with Symptomatic Gastroesophageal Reflux Disease).

The purpose of this statistical analysis plan (SAP) is to define the planned statistical methods consistent with the study objectives. This plan should be read in conjunction with the study protocol version 3.0 (14 September 2022) and the case report forms (CRFs) version 1.0 (Date: 16 November 2022). All analyses will be conducted using SAS® Version 9.4 or higher.

2. Objectives

2.1. Primary Objective

To evaluate the pharmacokinetic profile of vonoprazan (10 or 20 mg QD) in adolescent subjects with symptomatic GERD.

2.2. Safety Objective

To evaluate the safety of vonoprazan (10 or 20 mg QD) in adolescent subjects with symptomatic GERD.

2.3. Exploratory Objective

To evaluate symptom relief and pharmacodynamics of vonoprazan (10 or 20 mg QD) in adolescent subjects with symptomatic GERD.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 1, uncontrolled, randomized, open-label, parallel-group, multiple-dose study in adolescents aged 12 to 17 years with symptomatic GERD. Subjects will be screened for up to 28 days. Successfully screened subjects will be randomized to receive 10 or 20 mg of vonoprazan QD for 14 days. A total of 18 subjects will be enrolled into the study. Blood samples for pharmacokinetic testing will be collected on Days 7 and 14. If deemed clinically indicated by the principal investigator, gastric pH may be monitored for 24 hours on Day -1 and Day 7. The study will include 3 periods:

Screening Period (≤4 weeks): Subjects will undergo screening assessments to determine study eligibility, and baseline assessments will be performed. If all eligibility criteria are met, the subject will be randomized and enter the Treatment Period.
Treatment Period (Day 1 to Day 14): Subjects will be randomized to receive vonoprazan 10 mg or vonoprazan 20 mg QD.
Follow-up Period (2 weeks): A safety follow-up phone call will occur 2 weeks after the last dose of study drug to assess adverse events (AEs).

A subject will be considered to have completed the study if the subject completes the Treatment Period and the safety follow-up phone call. Following completion of study drug dosing or early discontinuation, the subject will be transitioned to local standard of care in accordance with each site's prespecified process.

The total duration of the study is up to 8 weeks. The Screening Period is up to 4 weeks, Treatment Period is 2 weeks, and safety follow-up phone call is 2 weeks after last study drug administration.

3.2. Study Endpoints

3.2.1. Pharmacokinetic Assessments

The primary vonoprazan pharmacokinetic endpoints will include the following parameters for each subject estimated from a population PK model:

- Maximum observed drug concentration at steady state ($C_{max,ss}$)
- Area under the plasma concentration-time curve during the dosing interval τ (AUC_{τ})
- Apparent oral clearance (CL/F)
- Apparent volume of distribution (V_z/F)

3.2.2. Efficacy and Pharmacodynamic Assessments

Efficacy and pharmacodynamic characteristics will be assessed by the following:

- The severity of GERD symptoms at screening and Days 7 and 14 as assessed by the investigator.

- The Pediatric Gastroesophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form (PGSQ-A-SF) symptom and impact subscale as assessed by the adolescent at screening and Days 7 and 14.
- Mean pH and percentage of time above pH 4, 5, and 6 at Day -1 and Day 7 in the subset of subjects for whom intragastric pH monitoring is performed when clinically indicated per the investigator.

3.2.3. Safety Assessments

Safety will be assessed by the following:

- AEs
- Laboratory test values (hematology, serum chemistry, urinalysis)
- Electrocardiograms
- Vital signs

3.3. Treatments

The pediatric doses for this study were selected to approximate equivalent adult exposures following administration of vonoprazan 10 or 20 mg QD and are age-based for adolescents 12 to 17 years of age. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to 1 of the following 2 groups during the Treatment Period:

- Vonoprazan 10 mg QD for 14 days
- Vonoprazan 20 mg QD for 14 days

3.3.1. Treatments Administered

Subjects will be instructed to take randomized study drug orally each morning between 7 and 10 am on an empty stomach with approximately 240 mL (8 oz) water. Subjects will take study drug at the clinic on Days 1, 7, 8, and 14; otherwise, study drug will be taken on an outpatient basis. Vonoprazan study medication will be supplied as 10 mg and 20 mg tablets.

4. General Statistical Considerations

In general, descriptive statistics will be presented by treatment group and by visit, as applicable. Continuous data will be summarized using descriptive statistics (i.e., n, mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be summarized using the subject count and percentage in each category. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported up to a maximum of 3 decimal places. Mean and median will be displayed to one level of precision greater than the data collected up to a maximum of 3 decimal places. Standard deviation and standard error (SE) will be displayed to two levels of precision

greater than the data collected up to a maximum of 3 decimal places. When count data are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment within the population of interest, unless otherwise specified. Refer to Appendix 1 for imputation rules for partial and missing AE onset dates as well as partial and missing prior/concomitant medication start and end dates. Data will be displayed in all listings sorted by treatment group.

4.1. Sample Size

Approximately 18 subjects will be enrolled with 9 subjects in each dose group. Attempts will be made to enroll an equal number of subjects between 12 to 15 and 16 to 17 years of age. Because this is a pharmacokinetic and safety trial with no comparator, there is no power determination affecting the sample size. The sample size of approximately 18 subjects is considered sufficient to assess the pharmacokinetics, safety, and tolerability of vonoprazan in a pediatric population aged 12 to 17 years. Fewer subjects may be enrolled based on preliminary data, if considered sufficient to adequately characterize the PK profile.

4.2. Randomization, Stratification, and Blinding

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to 1 of the following 2 groups during the Treatment Period:

- Vonoprazan 10 mg QD for 14 days
- Vonoprazan 20 mg QD for 14 days

An interactive response technology (IRT) system will be used to administer the randomization schedule. Randomization schedule will be generated using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for IRT, which will link sequential subject randomization numbers to treatment codes. The randomization will also use an appropriate block size, which will not be revealed.

This is an open-label study.

4.3. Study Day and Study Start Date

The screening period for the study will be from Day -28 to Day -1. The treatment period will be from Day 1 to Day 14 where the final Visit will be on Day 14. The Safety Follow Up period will be from Day 15 to Day 28.

For this study, randomization is to occur on Day 1, as well as the first dose of study drug. For assessments done on or after Day 1, study day is defined as assessment/event date - Day 1 + 1. For assessments done before Day 1, study day is defined as assessment/event date - Day 1.

4.4. Analyses set

4.4.1. Screened Set

The screened set will include all subjects who signed the study informed consent.

4.4.2. Enrolled Set

The enrolled set will include all subjects who signed the study informed consent and have been randomized.

4.4.3. Pharmacokinetic Set

The pharmacokinetic (PK) set will include all subjects who had at least one measurable concentration result. Where subjects experience issues which may affect exposure to study drug (e.g., emesis, dosing errors, etc.), data will be reviewed by the study pharmacokineticist and evaluated for exclusion from the PK population on a case-by-case basis. All subjects excluded from the PK population will be documented in the data listings.

4.4.4. Pharmacodynamic Set

The pharmacodynamic (PD) set will include subjects who receive at least 1 dose of study drug and have sufficient pH data to support calculation of pharmacodynamic parameters.

4.4.5. Safety Set

The safety set will include all subjects who receive at least 1 dose of study drug.

4.5. Visit Windows

All data summarized by visit will be based on the nominal visit name collected on the eCRF page. For data from unscheduled visits, these will be listed but not included in any by-visit summaries or analyses.

5. Subject Disposition

5.1. Disposition

Disposition will be summarized for all enrolled subjects by treatment and overall. The number and percentage of subjects who have been enrolled, have been treated (i.e., Safety Set), have completed the study treatment, have completed the study, have discontinued from the study treatment, have discontinued from the study, as well as the primary reason for study treatment discontinuation and study discontinuation (if applicable) will be tabulated.

Screen failures are defined as subjects whose legally authorized representative signs the informed consent form to participate in the clinical study but are not subsequently entered in the Treatment Period of the study. The number and percentage of screened, enrolled, and screen failure subjects, as well as the primary reason for screen failure will be

tabulated for all screened subjects. Subjects who fail screening and the reasons for screen failure will be listed for all screen failure subjects.

Additionally, a summary of the analysis sets will be provided to include the number and percentage of subjects in each analysis set by treatment group and overall. Subject disposition and analysis sets will also be presented in a listing.

5.2. Protocol Deviations

Protocol deviations will be recorded within the [redacted] Clinical Trial Management System (CTMS) and undergo cross-functional team review prior to database lock. In addition, protocol deviation classification (i.e., significant vs. not significant) as determined by Phathom Pharmaceuticals, Inc. prior to database lock will be documented in CTMS.

The number and percentage of subjects with significant protocol deviations will be summarized by CTMS activity subtype, treatment group and overall using the Safety set. Individual subject protocol deviations, both significant and non-significant, will be presented in a data listing using the Enrolled set.

6. Demographics and Baseline Characteristics

6.1. Demographics

Baseline demographics will be summarized by treatment and overall, for all subjects in the Safety Set. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, fertility status, height (cm), weight (kg), body mass index (BMI) (kg/m2), smoking status and alcohol use. Descriptive statistics will be presented for age, height and weight. Sex, race, ethnicity, smoking status, alcohol use, body mass index and fertility status will be summarized categorically. Demographic and baseline characteristics data will be listed for all subjects in the Safety Set.

6.2. Medical History

Medical history will be summarized by treatment and overall, for all subjects in the Safety Set. Medical history data will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The dictionary version used for reporting the study will be described in the relevant table and listing footnotes. Percentages will be calculated based on the number of subjects in the safety population. Medical history will be coded using MedDRA Version 23.0 or higher.

Medical history data including specific details will be presented in a listing.

6.3. Inclusion and Exclusion Criteria

The details of Inclusion and Exclusion criteria are listed in Section 4.1.1 and 4.1.2 of the protocol. All inclusion/exclusion criteria related information for enrolled subjects will be presented in a data listing. The listing will include those failed inclusion/exclusion criteria.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary. The WHO Drug Dictionary version used for reporting the study will be described in the relevant table and listing footnotes. If the medication start or end date is missing, it will be imputed before summary as described in Appendix 1. If the start date of a medication is completely missing and the end date is before dosing of study drug on Day 1, it will be counted as a prior medication. If the start date of a medication is completely missing and the end date is after dosing of study drug on Day 1, it will be counted as both a prior and concomitant medication. If the start date of a medication is on or after the dose of study drug on Day 1 and the end date of the medication is completely missing, it will be counted as a concomitant medication. Prior and concomitant medications will be summarized and listed based on the Safety Set.

7.1.1. Prior Medications

Prior medications are defined as those medications with a recorded end date before dosing of study drug on Day 1. The total number of prior medications will be summarized. The number and percentage of subjects with at least one prior medication will be summarized overall and by Anatomical Therapeutic Chemical (ATC) level 4 term and PT. Prior medications will be presented by treatment and overall using the Safety Set. PTs will be sorted in descending order of frequency within each ATC level 4 term based on counts in the overall column.

7.1.2. Concomitant Medications

Concomitant medications are defined as those medications that are taken after the first dose of study drug on Day 1. The total number of concomitant medications will be summarized in a table. The number and percentage of subjects with at least one concomitant medication will be summarized by ATC level 4 term and PT. Concomitant medications will be presented by treatment and overall using the Safety Set. PTs will be sorted in descending order of frequency within each ATC level 4 term based on counts in the overall column.

7.2. Study Drug

The study drug details related to study drug administration will be listed for each subject in the Safety Set.

7.3. Study Treatments

7.3.1. Extent of Exposure

Duration of exposure is defined as the total number of days a subject is exposed to any study drug and will be presented as the total number of days from the first dose date and time (Day 1) to the last dose date and time (date of last known study drug administration

minus the date and time of first dose + 1) as recorded on the Study Completion/Termination page on the eCRF. If the last dose date and time on the Study Completion/Termination page is missing, then the last dose date and time recorded on the Exposure page on the eCRF will be used. Duration of exposure will be categorized into time intervals and frequency counts and percentages will be presented for the number (%) of subjects in each interval. Percentages will be computed from the number of subjects in the Safety population. All summaries will be based on the Safety population. A listing on Extent of Exposure will also be presented based on Safety population.

7.3.2. Treatment Compliance

Subjects will be instructed to take randomized study drug orally between 7 and 10 am daily. Subjects will take study drug at the clinic on Days 1, 7, and 14; otherwise, study drug will be taken on an outpatient basis.

Treatment compliance overall and by treatment will be summarized using descriptive statistics. For each subject, the compliance will be calculated as the total number of actual doses divided by the total number of planned doses.

8. Efficacy Analysis

8.1. *Pharmacokinetic analyses*

A population PK model will be used to analyze the plasma concentration data, estimate pharmacokinetic parameters, and address the primary objective of this study. The planned analyses will be included in a separate document.

8.1.1. Plasma Concentrations

Blood samples will be collected at the following time points for PK assessment using a population PK approach:

- *Day 7: Pre-dose (within 30 mins prior to morning administration of Vonoprazan) and at, 0.5 to 2, and 2.5 to 4, hours after drug administration.*
- *Day 14: Pre-dose (within 30 mins prior to morning administration of Vonoprazan) and at 0.5 to 2 and 2.5 to 4 hours after drug administration*

Subjects enrolled prior to amendment 2 of the protocol had intensive blood collections intended to be used for Non-compartmental PK analyses. Those samples were collected at different scheduled times than described above but will still be used in the population PK analyses.

Individual plasma concentrations will be presented in data listings with their scheduled collection times based on the protocol under which they were enrolled.

8.2. Exploratory analyses

GERD Symptom Assessment and PGSQ-A-SF will be presented using the Safety Set. The Pharmacodynamic assessment will be analyzed with Pharmacodynamic Set.

Prior to Protocol Amendment 2, the GERD Symptom Assessment and PGSQ-A-SF were scheduled for Day 8. Amendment 2 changed the schedule for these assessments to Day 7. Summaries and analyses will be presented together as Day 7/8.

8.2.1. GERD Symptom Assessment

The GERD Symptom Assessment-Investigator scale evaluates 5 symptoms of GERD: heartburn, acid regurgitation, dysphagia, belching and epigastric pain. The maximum severity of each GERD symptom occurring during the 7 days prior to the study visit will be assessed. The severity for each symptom will be recorded as either none, mild, moderate, severe or very severe. The severity of GERD symptoms at baseline and Days 7 and 14 as assessed by the investigator will be summarized overall and by vonoprazan dose.

8.2.2. PGSQ-A-SF

The symptom subscale measures the number of days over the past 7 days on which subjects experience each individual symptom, where 1=0 days; 2=1 or 2 days; 3=3 or 4 days; 4=5 or 6 days; and 5=every day (7 days). Mean symptom subscale score is the mean of the 7 individual symptom item scores. The impact subscale measures the impact of symptoms on school, family, and social activities in the past 7 days, where 1=never; 2=almost never; 3=sometimes; 4=almost always; and 5=always. Mean impact subscale score is the mean of the 4 individual impact item scores.

The change from baseline to Days 7 and 14 in the PGSQ-A-SF symptom and impact subscale, as assessed by the adolescent will be summarized overall and by vonoprazan dose.

8.2.3. Pharmacodynamic Assessment

Mean pH and percentage of time above pH 4, 5, and 6 at Day -1 and Day 7 will be summarized for the subset of subjects for whom intragastric pH monitoring is performed when clinically indicated per the investigator.

The investigator reported clinical criteria that supported the need for 24-hour gastric pH monitoring in individual subjects will be presented in a data listing.

9. Safety Analysis

Safety will be assessed based on AEs, SAEs, physical examination findings, vital sign measurements, ECG results, and clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis All safety analyses will be conducted for the Safety Set.

9.1. Adverse Events

Adverse events will be coded using Version 24.0 or higher of the Medical Dictionary for Regulatory Activities (MedDRA). An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality or relationship to the drug. A treatment-emergent adverse event (TEAE) is defined as any event that occurs after the first dose of study drug or any event at baseline that worsens in either intensity or frequency after the first dose of study drug in that period. A PTE is defined as any untoward medical occurrence in a clinical investigation subject whose informed consent to participate in a study has been signed, which has occurred prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

Overall AEs will be summarized separately, for the following adverse events.

- Treatment-Emergent Adverse Event
- Serious Treatment-Emergent Adverse Event
- Study Drug-Related Treatment-Emergent Adverse Event
- Study Drug-Related Treatment-Emergent Serious Adverse Event
- Treatment-Emergent Adverse Event Leading to Treatment Discontinuation
- Treatment-Emergent Adverse Event Leading to Study Discontinuation
- Adverse Event Leading to Death

A subject with multiple adverse events within a primary SOC or preferred term will only be counted once towards the total for that SOC and/or preferred term. For the AE severity and relationship summaries, if a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity or relationship will be presented. If a subject reported more than one adverse event within the same primary SOC, then the subject will be counted only once with the greatest severity or relationship at the SOC level. For table summaries if severity is missing then ‘severe’ is assumed. If relationship is missing, relationship to study drug is assumed to be ‘related’.

The number and percentage of subjects with TEAEs will be summarized by treatment in the following ways:

- by primary SOC and preferred term
- by primary SOC, preferred term and maximum severity
- by primary SOC, preferred term and relationship to study drug

The number and percentage of subjects with TEAEs related to study drug will be summarized by treatment in the following ways:

- by primary SOC and preferred term
- by primary SOC, preferred term and maximum severity

The number and proportion of subjects as well as the number of events (except deaths) with the following types of events will be summarized by primary SOC, preferred term and treatment group:

- Adverse events leading to treatment discontinuation
- Adverse events leading to study discontinuation
- Serious Adverse Events (SAEs)
- Deaths
- Adverse events of special interest (AESI)

All adverse events will be included in a listing using the safety set. Pre-treatment AEs and Serious AEs will be listed using the Screened set. In addition, the following select adverse events will be displayed in separate listings:

- Deaths
- Serious adverse events
- Adverse events leading to treatment discontinuation
- Adverse events leading to study discontinuation
- Adverse events of special interest

9.1.1. Adverse Events of Special Interest (AESI)

The number and percentage of subjects with TEAEs and SAEs that are in one of the AESI categories presented in Table 1 will be summarized by AESI category, primary SOC and preferred term. The search criteria that will be used to identify AESIs are specified in the table.

Table 1: Adverse Events Special Interest – Search Criteria

Adverse Event of Special Interest	Search Criteria
Clostroides difficile enteric infection	Pseudomembranous colitis SMQ (Narrow)
Bone Fracture	Bone Fracture Custom Query (PTs defined below) Acetabulum fracture Ankle fracture Atypical femur fracture Atypical fracture Avulsion fracture Bone fissure Bone fragmentation Chance fracture Clavicle fracture Comminuted fracture Complicated fracture Compression fracture Craniofacial fracture Epiphyseal fracture Facial bones fracture Femoral neck fracture Femur fracture Fibula fracture Foot fracture Forearm fracture Fracture Fracture blisters Fracture displacement Fracture malunion Fracture nonunion Fracture of clavicle due to birth trauma Fractured coccyx Fractured ischium Fractured sacrum Greenstick fracture Hand fracture Hip fracture Humerus fracture Ilium fracture Impacted fracture Jaw fracture Limb fracture Lower limb fracture Fractured skull depressed Lumbar vertebral fracture Metaphyseal corner fracture Multiple fractures Open fracture Osteoporotic fracture Patella fracture Pathological fracture Pelvic fracture Pubis fracture Radius fracture Rib fracture Sacroiliac fracture Scapula fracture Skull fracture Skull fractured base Spinal compression fracture Spinal fracture Spinal fusion fracture Sternal fracture Stress fracture Subchondral insufficiency fracture Thoracic vertebral fracture Tibia fracture Torus fracture Traumatic fracture Ulna fracture Upper limb fracture Wrist fracture
Severe cutaneous adverse reactions, including hypersensitivity	Severe cutaneous adverse reactions SMQ (Narrow)
Hepatotoxicity	• Drug related hepatic disorders - comprehensive search (SMQ) (Narrow) • Cholestasis and jaundice of hepatic origin (SMQ) (Broad) • Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (Broad) • Hepatitis, non-infectious (SMQ) (Broad) • Liver related investigations, signs and symptoms (SMQ) (Narrow)

MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SMQ: Standardized MedDRA Queries.

9.2. Clinical Laboratory Evaluations

Safety lab parameters, including clinical chemistry, hematology and urinalysis will be presented at Screening, Day 7 and 14.

Descriptive statistics for clinical laboratory values (hematology, chemistry and urinalysis laboratory tests) will be presented. Changes from baseline will also be presented for quantitative variables. For categorical variables (i.e., normal or abnormal findings, or qualitative clinical laboratory tests), shift tables for the change from baseline to the end of study will be presented. Results of clinical laboratory values will be categorized as low, normal, or high according to laboratory range specifications. Shifts from baseline to each scheduled post-baseline time point will be presented to show the number and percentage of subjects in each category by parameter.

9.2.1. Clinical chemistry

Abnormal liver function tests are defined as liver test values that meet at least one of the criteria listed below. The number and percentage of subjects with at least one post-baseline abnormal liver function test and with the test value higher than baseline value, if available, will be presented. A supportive listing of subjects with such post-baseline elevations will be provided including the subject ID, baseline, and post baseline values.

- ALT > 3xULN
- ALT > 5xULN
- ALT > 10xULN
- ALT > 3xULN and Total Bilirubin > 2xULN

- AST > 3xULN
- AST > 5xULN
- AST > 10xULN
- AST > 3xULN and Total Bilirubin > 2xULN

- Total Bilirubin > 2xULN

- AST > 3xULN or ALT > 3xULN

- AST > 5xULN or ALT > 5xULN

- AST > 10xULN or ALT > 10xULN

- (AST > 3xULN or ALT > 3xULN) and Total Bilirubin > 2xULN

- AST > 3xULN and ALT > 3xULN

- AST > 5xULN and ALT > 5xULN

- AST > 10xULN and ALT > 10xULN

- AST > 3xULN and ALT > 3xULN and Total Bilirubin > 2xULN

- Alkaline phosphatase > 1.5xULN
- ALT > 3xULN and Alkaline phosphatase > 1.5xULN
- AST > 3xULN and Alkaline phosphatase > 1.5xULN

- Alkaline phosphatase > 3xULN
- ALT > 3xULN and Alkaline phosphatase > 3xULN
- AST > 3xULN and Alkaline phosphatase > 3xULN

- ALT or AST >3xULN and a 2-fold increase above baseline for subjects with normal baseline ALT or AST levels
- ALT or AST > 8xULN for subjects with normal baseline ALT or AST levels

9.2.2. Urinalysis

Microscopic urinalysis results will be listed only. All laboratory data test results will be included in data listings.

9.3. Vital Sign Measurements

Summary tables will be presented by treatment for vital sign data, including height (cm), weight (kg), heart rate (beats/min), sitting systolic blood pressure (mmHg), sitting diastolic blood pressure (mmHg), respiratory rate (breaths/min), and temperature (C) (and route used to measure temperature i.e., Oral, Tympanic or Temporal) in the Safety Set. Observed results and change from baseline to each scheduled post-baseline time point will be presented. Change from baseline will only be calculated for subjects having non-missing baseline and post-baseline measurements. The height assessment will only be done at the Screening visit. All vital signs data will be presented in a listing.

Abnormal vital sign values are defined as vital sign values that meet one of the criteria listed below. The number and percentage of subjects with at least one post-baseline abnormal vital sign value and with the value worse than the baseline value, if available, will be presented. A supportive listing of subjects with such post-baseline elevations will be provided including the subject ID, baseline, and post-baseline values.

- Systolic blood pressure (mmHg):
  - <50
  - >180
- Diastolic blood pressure (mmHg):
  - <50
  - >100
- Heart rate (bpm):

- <50
- >120

9.4. Physical examination

All data collected from physical examinations assessment must be available in the source documents but will not be added to the analysis database.

9.5. Electrocardiogram results

An overall 12-lead ECG interpretation (Normal, Abnormal – Not Clinically Significant, Abnormal –Clinically Significant) will be available based on central reading of ECG data. Shifts from baseline to each scheduled post-baseline time point will be presented to show the number and percentage of subjects in each category by treatment for subjects in the Safety Set.

Abnormal QTcF values are defined as ECG values that meet at least one of the criteria listed below. The number and percentage of subjects with at least one of the post-baseline abnormal values and with post-baseline value higher than baseline value, if available, will be presented using the Safety set. A supportive listing of subjects with such post-baseline elevations will be provided including the subject ID, baseline, and post-baseline values.

- Absolute QTcF interval prolongation:
  - QTc interval > 450 msec
  - QTc interval > 480 msec
  - QTc interval > 500 msec
- Change from baseline in QTcF interval:
  - QTc interval increases from baseline >30 msec
  - QTc interval increases from baseline >60 msec
  - QTc interval > 450 msec with increase from baseline >30 msec

Results for heart rate, R-R interval, P-R Interval, QRS Interval, QT Interval, QTcF Interval, Rhythm, Arrhythmia or Conduction defects, Evidence of Myocardial Infarction, ST-segment abnormality, T-wave abnormality, and U-wave will be listed only.

9.6. Pregnancy test

Pregnancy test results will be presented in a listing for the Safety Set.

10. Interim Analysis/Other Analysis

10.1. Interim Analysis

No formal interim analyses will be performed in this study.

10.2. Coronavirus Pandemic

In accordance with guidance issued by regulatory agencies, study data collection will document visits missed/delayed due to COVID-19 related reasons and assessments completed via alternative method due to COVID-19 related reasons.

The COVID-19 impacts on individual subjects collected on the COVID-19 CRF pages will be listed for the Enrolled Set. Protocol deviations related to COVID-19 will be marked in the protocol deviation listing for the Enrolled Set.

The anticipated impact of COVID-19 is widely regarded as unknown. If the impact of COVID-19 on the conduct of this study is observed to be significant, further summaries and listings of the impact will be explored.

11. Changes in the Planned Analysis

Not Applicable

12. Appendices

12.1. Appendix 1: Imputation Algorithm for Partial and Missing Dates

12.1.1. Rules for Concomitant Medication Start Date Imputation

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of study drug, then the day and month of the date of the first dose of study drug will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of study drug, then 31 December will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of study drug, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of study drug, then the day of the date of the first dose of study drug will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of study drug or if both years are the same but the month is before the month of the date of the first dose of study drug, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of study drug or if both years are the same but the month is after the month of the date of the first dose of study drug, then the first day of the month will be assigned to the missing day.

12.1.2. Rules for Concomitant Medication End Date Imputation

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date. If the non-imputed stop date is more complete than the non-imputed start date (e.g., stop date has a missing day and start date has missing month or stop date has full date but the start date has missing day or month) then the stop date will be imputed (as per rules below) and the start date will be imputed with the end date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of study drug, then the day and month of the date of the last dose of study drug will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of study drug, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of study drug, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of study drug, then the day of the date of the last dose of study drug will be assigned to the missing day.
- If either the year is before the year of the date of the last dose of study drug or if both years are the same but the month is before the month of the date of the last dose of study drug, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last dose of study drug or if both years are the same but the month is after the month of the date of the last dose of study drug, then the first day of the month will be assigned to the missing day.

12.1.3. Rules for Prior Medication Start Date Imputation

For prior medications, incomplete (i.e., partially missing) start dates will be imputed and will follow the same rules as in Section 12.1.1.

12.1.4. Rules for AE Start Date Imputation

For AEs, incomplete (i.e., partially missing) start dates will be imputed and will follow the same rules as in Section 12.1.1. Incomplete stop dates will not be imputed.

12.2. Appendix 2: Schedule of Events

	Screening Period		Treatment Period			Final Visit	Safety FU	
Timing	**Day -28 to Day -2**	**Day-1 [a]**	**Day 1**	**Day 7**	**Day 8 [a]**	**ET Day 14**	**Phone Call Day 28**	**Unscheduled Visit [b]**
Visit Number:	1	2	3	4	5	6	7	
Informed consent [c]	X							
Inclusion/exclusion criteria	X	X	X					
Demographic and medical history	X							
Smoking status and alcohol use	X							
Medication history	X							
Physical examination [d]	X			X		X		X
Vital signs [e]	X		X	X		X		X
Weight and height [f]	X			X		X		
Concomitant medications	X	X	X	X	X	X	X	X
Concurrent medical conditions	X							
Hepatitis B and C; HIV [g]	X							
Urine drug screen [h]	X							
Clinical laboratory tests [i]	X			X		X		X
Pregnancy test [j]	X			X		X		
Guidance on avoidance of pregnancy	X			X		X		
12-lead electrocardiogram [k]	X			X		X		
GERD Symptom Assessment-Investigator	X			X		X		
PGSQ-A-SF	X			X		X		
Randomization [l]			X					
Dispense study drug [m]			X	X				
Study drug administration [m]			X	X				

In-patient check in/out [n]		X	X	X	X			
24-hour Gastric pH monitoring [o]		X		X				
PK blood sample collection [p]				X		X		
Drug return/accountability				X		X		
AE/pretreatment event assessment [q]	X	X	X	X	X	X	X	X

AE: adverse event; ET: early termination; FU: follow-up; GERD: gastroesophageal reflux disease; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus, PGSQ-A-SF: Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form; PK: pharmacokinetic

a. Visit 2 and Visit 5 only required for subjects undergoing gastric pH monitoring at select sites.
b. At an unscheduled visit, the following procedures are to be completed with additional procedures at the investigator's discretion: a brief physical examination, vital sign measurements, concomitant medication assessment, AE assessment, and clinical laboratory tests. If the visit results in premature termination, then all procedures outlined for the final visit should be performed.
c. Informed consent will be signed by the subject's legally authorized representative prior to any activity in the study. Subject assent (if applicable) may be obtained as required per site guidelines.
d. A complete physical examination will be performed at screening (at minimum, assessment of skin, cardiovascular, respiratory, gastrointestinal, and neurological systems). A brief physical examination will be performed at other visits (at minimum, assessment of skin, cardiovascular, respiratory, and gastrointestinal systems). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.
e. Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature.
f. Height collected only at screening.
g. Hepatitis B surface antigen, hepatitis C virus antibody, and HIV type 1 and 2 antibodies.
h. Urine drug/alcohol screen will occur at screening per the site standard procedures.
i. Clinical laboratory testing will include hematology, serum chemistry, and urinalysis. Glucose will be obtained after an 8-hour fast at all visits. Blood draws should follow vital signs or electrocardiograms.
j. Only female subjects with childbearing potential will have urine hCG; if positive, confirm with serum hCG.
k. Single 12-lead electrocardiogram recordings will be made after the subject has been in the supine position for at least 5 minutes at screening. A single repeat measurement is permitted at screening for eligibility determination. Measurements of the following intervals will be reported: PR interval, RR interval, QRS interval, and QT interval. The QT interval adjusted for heart rate will be derived in the electronic database from the RR and QT intervals, using the Fridericia method. Assessments should include comments on whether the tracings are normal or abnormal (if abnormal, whether clinically significant or not clinically significant); rhythm; the presence of arrhythmia or conduction defects; any evidence of myocardial infarction; and ST-segment, T-wave, and U-wave abnormalities.
l. Subject will be randomized to study treatment after all eligibility criteria have been met.
m. Subjects will self-administer study drug, possibly with assistance from the parent/caregiver. Study drug will be dispensed and administered in the clinic on Days 1, 7, and 14. Study drug for at-home administration will be dispensed on Day 1 (to be taken on Days 2-6) and Day 7 (to be taken on Days 8-13). Study drug should be taken every day between 7 and 10 am on an empty stomach. The exact time of dosing on Day 6 and Day 13, if the dose was taken on an empty stomach should be noted by the subject or parent/caregiver and recorded by clinic staff upon arrival at the clinic. Subjects will be instructed not to eat any food or take study drug on the morning of Days 7 and 14 prior to their arrival at the clinic. If a subject consumes any food prior to the dose on Days 6 and 13 or prior to arrival at the clinic on Days 7 or 14, the time and content of the meal is to be noted and recorded in the eCRF by clinic staff. On Days 7 and 14, water is permitted as desired except for the period 1 hour before and 1 hour after administration of study drug (other than as permitted for study drug dosing). Subjects will be provided a meal 30-60 minutes after study drug dosing on Days 7 and 14 per the clinic's standard procedures.
n. Check in on Day -1 and Check out on Day 1 and Check in on Day 7 and Check out on Day 8 (as determined by PI) is only for subjects who will undergo 24-hour gastric pH monitoring.
o. Gastric pH monitoring on Day -1 for 24 hours and on Day 7 for 24 hours; only if clinically indicated.
p. Blood samples for PK analysis of vonoprazan in plasma will be collected on Days 7 and 14. On both days, one pre-dose sample will be collected prior to the morning administration of vonoprazan and two additional samples will be collected after drug administration: one between 0.5 and 2 hours post-dose and one between 2.5 and 4 hours post-dose. The exact time of each pharmacokinetic sample should be recorded in the source and eCRF.
q. Collection of pretreatment events will start after the informed consent form has been signed. Adverse events will be assessed from time of informed consent signing until the follow-up visit and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

12.3. Appendix 3: GERD Symptom Assessment-Investigator

The following 5 symptoms of GERD will be evaluated.

Symptom	**Definition**
Heartburn	A burning feeling in the mid-epigastric area and/or chest
Acid regurgitation	Flow of sour or bitter fluid into the mouth
Dysphagia	Difficulty in swallowing
Belching	The voiding of gas from the stomach through the mouth, which may have been associated with acid regurgitation
Epigastric pain	Central upper abdominal pain

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The maximum severity of each GERD symptom occurring during the 7 days prior to the study visit will be assessed as detailed below.

Severity	**Definition**
None	No symptom
Mild	Symptom did not last long and was easily tolerated
Moderate	Symptom caused discomfort and/or interrupted usual activities (including sleep)
Severe	Symptom caused great interference with usual activities and may have been incapacitating (including sleep)
Very severe	Symptom caused intense and constant discomfort and/or marked interference with usual activities (including sleep)